Partial Area Under Curve (pAUC): Product-Specific Guidance Development

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Partial Area Under Curve (pAUC)

- For two products to be considered bioequivalent, there should be no significant difference in the rate and extent of absorption of the active moiety, which are usually measured by Cmax (the maximum drug concentration) and AUC (the area under the concentration-time curve), respectively.

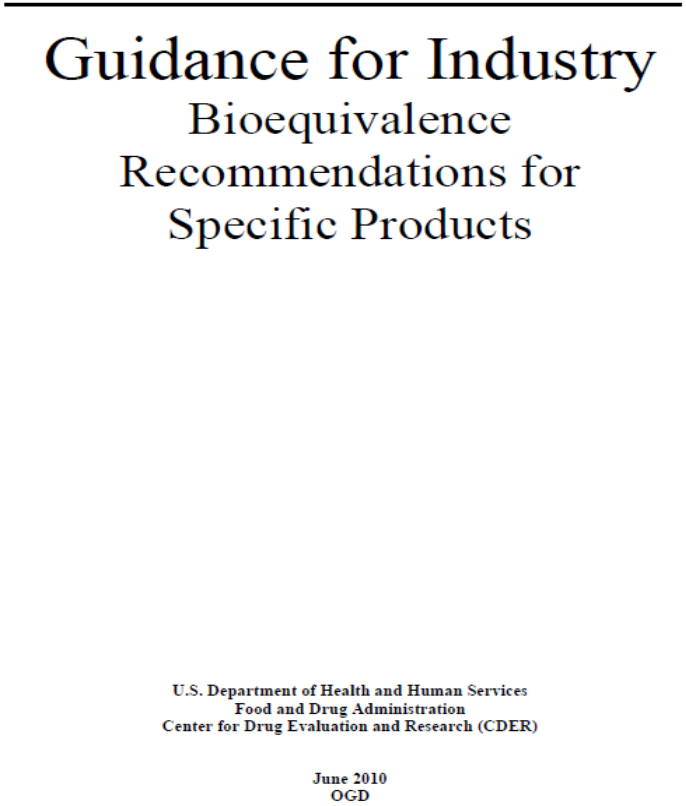
- For some products with complex pharmacokinetic (PK) profiles, the traditional metrics of AUC and Cmax may not be sufficient to ensure therapeutic equivalence.

- An additional PK metric, such as a pAUC to assess exposure during particular time interval(s), may be necessary to assess potential differences in bioavailability (BA) or bioequivalence (BE).

Regulatory History of pAUC (FDA)

- Year 2010: Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting
  - Modified Release (MR) products: multiphasic drug release
- Year 2013 FDA draft guidance "Bioequivalence Studies with PK Endpoints for Drugs Submitted Under an ANDA" and Year 2019 draft guidance "Bioavailability Studies Submitted in NDAs or INDs: General Considerations"
  - The use of partial AUC as an early exposure measure under certain circumstances. The time to truncate the partial area should be related to a clinically relevant pharmacodynamic (PD) measure
- Product-Specific Guidances (PSGs) for generic drug development recommending pAUC
- Year 2018: Initiation of CDER-wide efforts regarding pAUC

Product-Specific Guidances (PSGs)


Guidance for Industry

Bioequivalence Recommendations for Specific Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2010
OGD

- Provide drug-specific recommendations for demonstrating BE between test and reference drug products: study design, strengths, study population, analytes to measure, dissolution method, and other special considerations
- Enhance transparency between the FDA and generic drug industry
- Reduce industry inquiries on BE recommendations
- Improve quality of submitted ANDAs (i.e., faster approval times)
- Promote FDA's generic drug approval process

CDER Efforts Regarding pAUC

- Discuss and address questions related to use and determination of appropriate pAUC metric for BE assessment to ensure efficacy and safety of new and generic products

- Develop a consistent regulatory approach to determining pAUCs

- Provide harmonized and consistent pAUC recommendations applicable to both new and generic drugs

Framework for pAUC in BE Assessment

1. Clinical relevance of proposed pAUC
   i. Quick onset of drug effect (e.g., Naloxone HCl nasal spray)
   ii. Shape of the PK profile affects the clinical performance (e.g., Methylphenidate HCl ER capsules)

2. Product formulation-related characteristics
   i. Multi-phasic release characteristics (e.g., Zolpidem ER tablets)
   ii. Abuse-deterrent formulation (e.g., Hydrocodone bitartrate ER tablets)
   iii. Locally-acting drug products where systemic PK serves as a surrogate of local drug delivery (e.g., Mesalamine ER capsules)

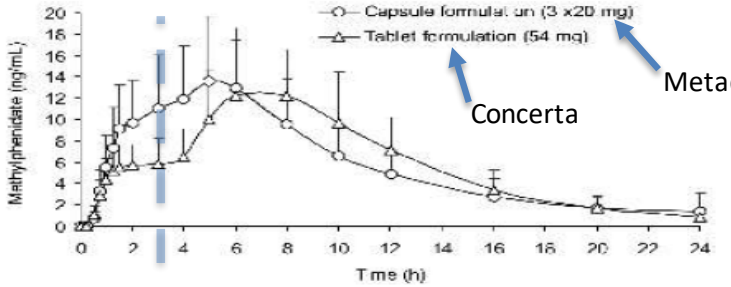
3. Other considerations
   i. Multiple indications with different dosing frequencies (e.g., Scopolamine TDS)

ER: extended release; TDS: transdermal delivery system

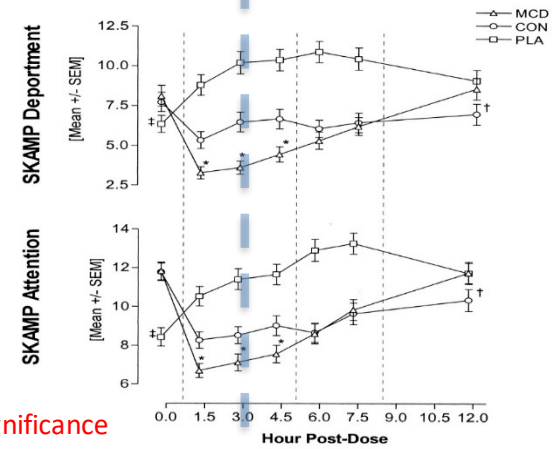
Shape of PK Profile: Methylphenidate (MPH) Extended Release (ER) Products

Indicated for attention deficit hyperactivity disorder (ADHD)

Strong PK/PD link: differences in PK is reflected in the SKAMP (**S**wanson, **K**otkin, **A**gler, **M**-Flynn, and **P**elham Rating Scale) ratings over clinically relevant time windows



Gonzalez, M. A., et al. "Methylphenidate bioavailability from two extended-release formulations." *International journal of clinical pharmacology and therapeutics* 40.4 (2002): 175-184.



MCD = Metadate CD
CON = Concerta
PLA = placebo

Swanson, James M., et al. "A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study)." *Pediatrics* 113.3 (2004): e206-e216.

* and †: statistically significance between active treatments

PSG for MPH Orally Disintegrating ER Tablets

- The shape of PK profile is clinically important
- pAUC Recommendation: $pAUC_{0\text{-}3/4hr}$, $pAUC_{3/4\text{-}7/8hr}$ and $pAUC_{7/8\text{-}12hr}$
- Comparable drug exposures over clinically relevant time windows to ensure therapeutic equivalence

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Methylphenidate_draft_Orally%20disintegrating%20tab%20ER_RLD%20205489_RC07-18.pdf

Abuse-Deterrent Opioid Products

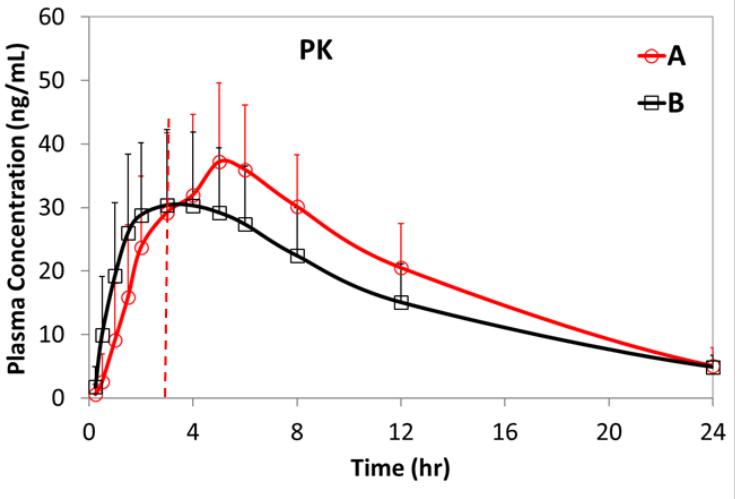
- Indicated for severe pain relief
- Opioid epidemic: Development of abuse-deterrent formulation (ADF) is one of several steps to fight this epidemic.

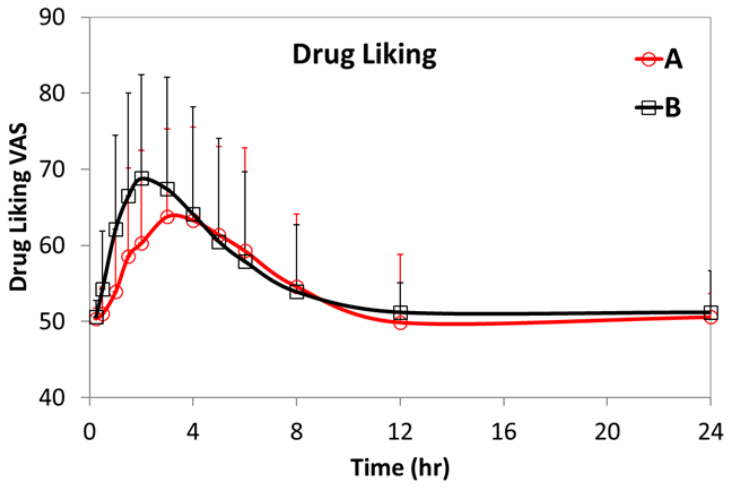
NDA #	API	Trade Name	Approval date	Dosage Form	Labeling for Abuse Deterrence
022272	Oxycodone	**OxyContin**	04/05/10	ER Tablet	IV, IN
022321	Morphine/Naltrexone	**Embeda**	10/17/14	ER Capsule	IN, Oral (crushed)
206627	Hydrocodone	**Hysingla ER**	11/20/14	ER Tablet	IV, IN, Oral (chewed)
206544	Morphine	**MorphaBond ER**	10/02/15	ER Tablet	IV, IN
208090	Oxycodone	**Xtampza ER**	04/26/16	ER Capsule	IV, IN
208603	Morphine	**Arymo ER**	01/9/2017	ER Tablet	IV, IN
209777	Oxycodone	**RoxyBond**	04/20/2017	Tablet	IV, IN

IV: intravenous; IN: intranasal

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics

Traditional PK Metrics May not Ensure Similar Abuse Deterrence for ADF

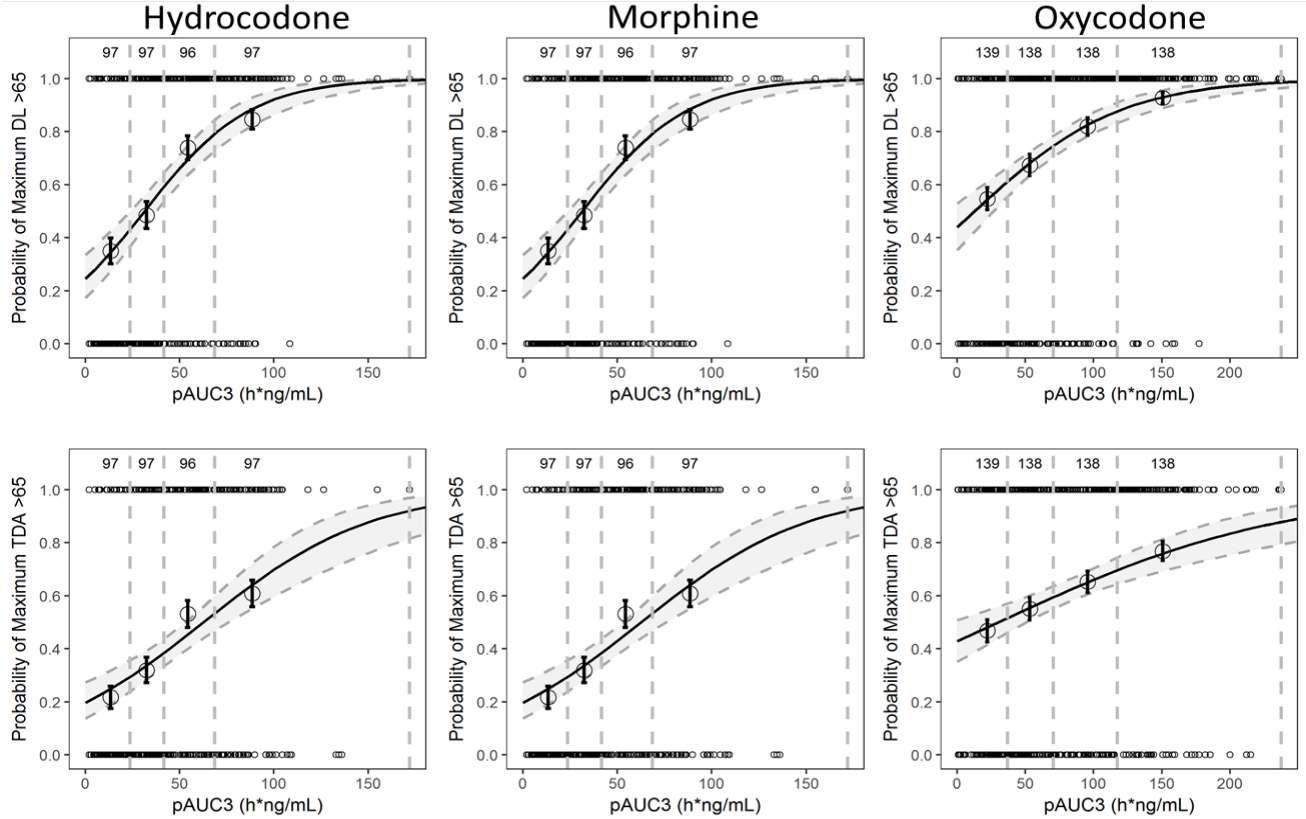




- Branded Industry Working Group (BIWG) commented that Product A had a greater Cmax, but produced smaller maximum drug liking (MAXDL) based on drug liking Visual Analogue Scale (**VAS**) score compared to Product B

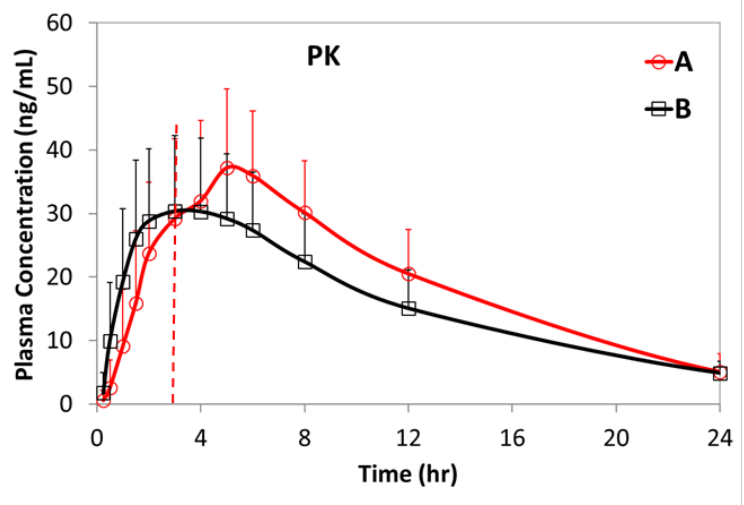
PK/PD curves adapted from the presentation by Jeffrey M. Dayno in 2016 FDA Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products (https://www.fda.gov/Drugs/NewsEvents/ucm509853.htm)

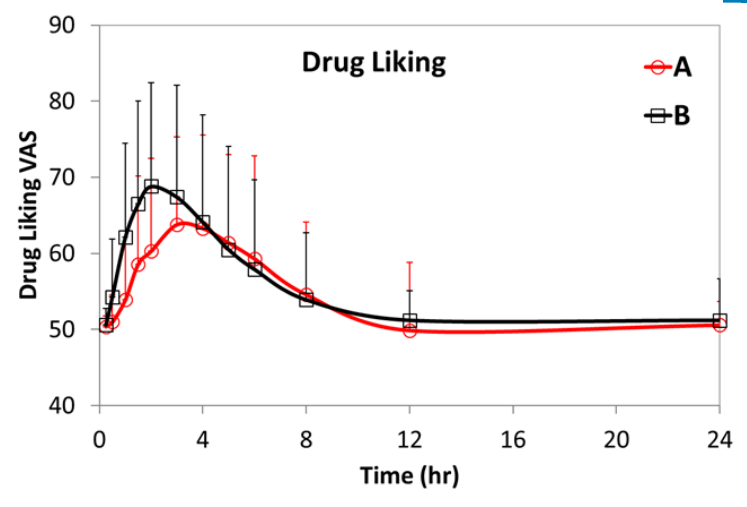
Probability of MAXDL/MAXTDA>65 is Correlated with $pAUC_{0\text{-}3h}$



MAXDL: maximum drug liking VAS score; MAXTDA: maximum take drug again VAS score
Adapted from presentation by Liang Zhao at 2019 ASCPT Annual Meeting

Use of Early pAUC to Link PK & Drug Liking





- BIWG commented that Product A had a higher Cmax, but produced smaller MAXDL compared to Product B
- Geometric mean ratio (A/B)
  - $pAUC_{0\text{-}3h}$: 0.66 (90% CI: 56.49-76.48%)

PK/PD curves adapted from the presentation by Jeffrey M. Dayno in 2016 FDA Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products (https://www.fda.gov/Drugs/NewsEvents/ucm509853.htm)

PSG for Abuse-Deterrent Formulation

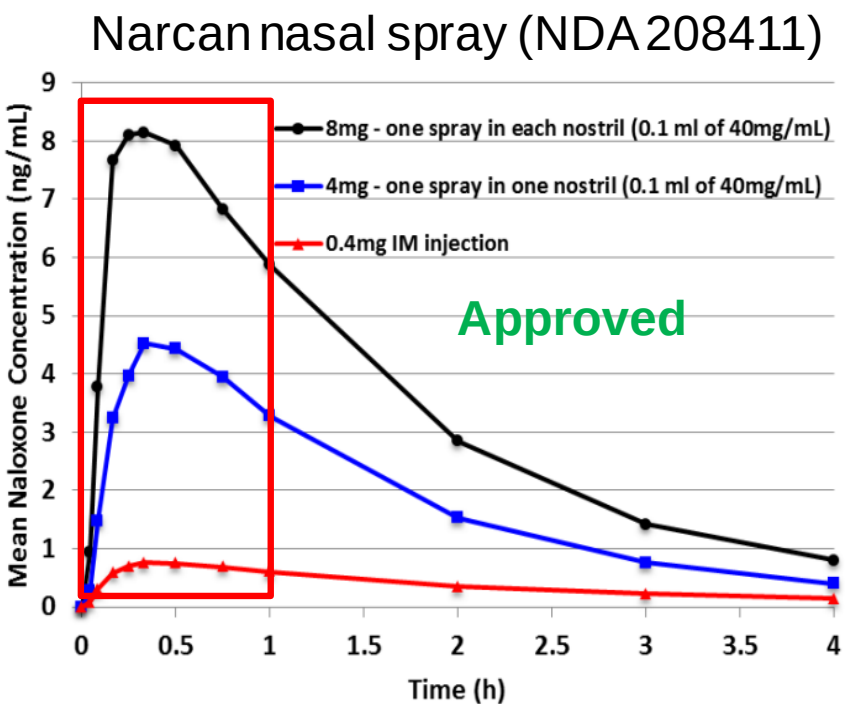
- Early drug exposures are recommended to establish that a generic abuse-deterrent opioid product is no less abuse-deterrent than its reference product
  - Early pAUC values are no greater

- pAUC Recommendation: Applicants should submit pAUCs (e.g., AUC0-3 hours and AUC0-4 hours) as supportive data

- pAUC recommendation included in 7 PSGs for morphine, oxycodone, and hydrocodone ADF products

Naloxone Hydrochloride Nasal Spray

- Initial approval in 1971 (Narcan, NDA 016636) for intravenous, intramuscular, and subcutaneous injection for complete or partial **reversal of opioid depression/opioid overdose**
- Nasal sprays applications submitted via 505(b)(2)
- PK study submitted to establish a scientific bridge to the Agency's prior findings of efficacy and safety for Narcan injection
  - Concentrations at early time points were evaluated to ensure quick onset of action



https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000ClinPharmR.pdf

PSG for Naloxone Nasal Spray

- The onset of action is critical for reversal of opioid overdose

- Comparable systemic exposure at early time points as supportive evidence for quick reversal of opioid overdosing

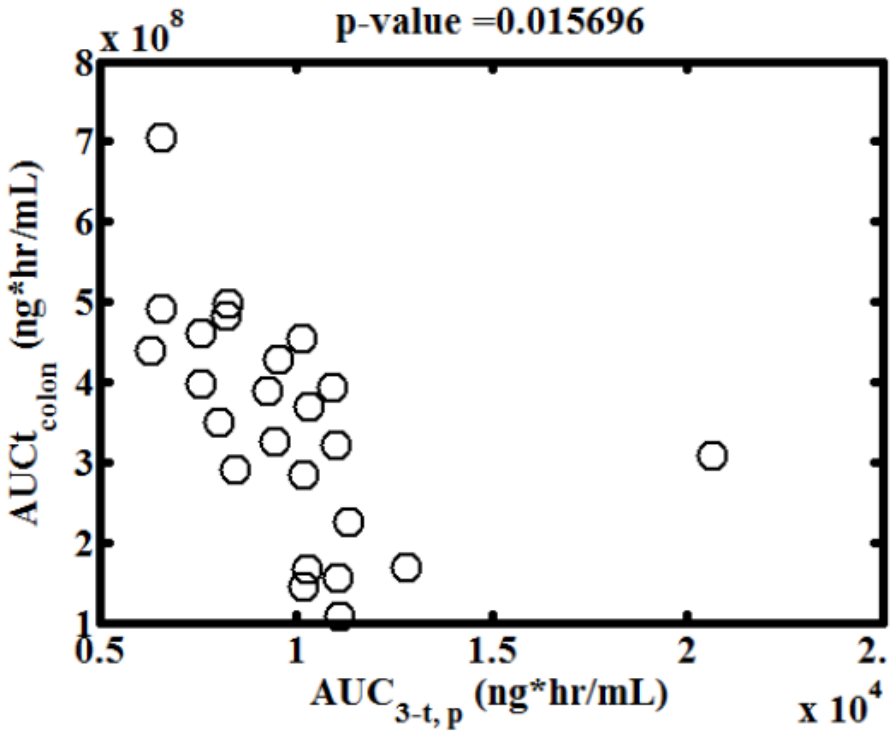
- pAUC Recommendation: $pAUC_{0\text{-}4min}$, $pAUC_{0\text{-}10min}$ and $pAUC_{10\text{-}30min}$

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Naloxone%20hydrochloride_%20nasal%20spray_%20NDA%20208411_RC04-17.pdf

Mesalamine ER Capsules

- Indicated for the maintenance of remission of ulcerative colitis in adults.
- Mechanism of action of mesalamine (5-ASA) is believed to be **local** to the intestinal mucosa rather than systemic.
- It takes about 3 hours for the drug to reach the target region of gastrointestinal (GI) tract.
  - Local equivalence (particularly drug delivery to the colon) is important.

Predicted Colon Availability Correlates with Systemic Exposure Post 3 Hours



Slides courtesy: Xinyuan (Susie) Zhang, Ph.D.

PSG for Mesalamine ER Capsules

- PK endpoint study is a reasonable surrogate to reflect GI local delivery/availability
  - Colon drug exposures correlate with systemic $pAUC_{3\text{-}t}$

- pAUC Recommendation: Applicants should submit pAUCs (e.g., $AUC_{0\text{-}3hr}$ and $AUC_{3hr\text{-}t}$) as supportive data

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mesalamine_draft_Oral%20cap%20ER_RLD%2020049_RC10-17.pdf

Summary

- CDER has created a center-wide framework to increase coordination between offices for the standards applied to new drug and generic drug approval
  - Case examples provided

- It is challenging to prospectively identify the need for pAUC
  - Exposure-Response information may be unavailable to assess the clinical relevance of pAUC recommendations
  - The use of pAUC may be product-specific

- FDA strives to provide harmonized and consistent pAUC recommendations applicable to both new and generic drugs

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pAUC WG

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- Yih-Chain Huang
- Caliope Sarago
- Steven Chopski


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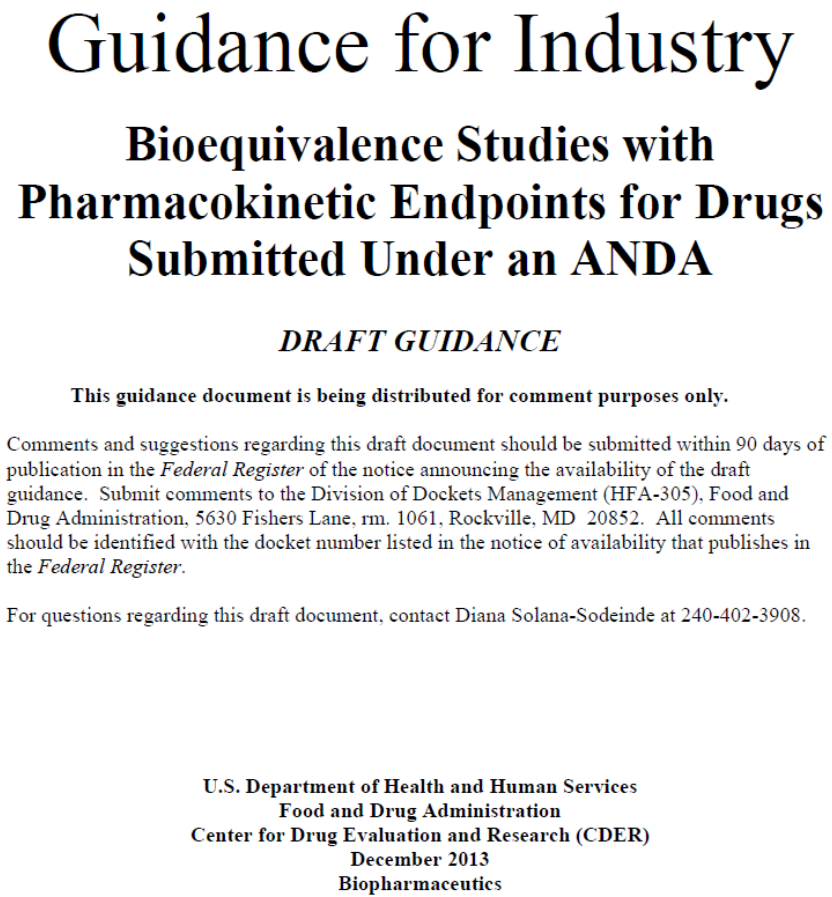
ADMINISTRATION

General Guidance on PK Endpoints for BE



Guidance for Industry

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Diana Solana-Sodeinde at 240-402-3908.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2013
Biopharmaceutics

- Draft guidance issued December 2013
- Scope: applies to oral and non-oral (e.g., transdermal) drug products in which reliance on systemic exposure measures is suitable for documenting BE
- Covers aspects of BE study design, study population, and specific recommendations for specific dosage forms including cases in which BE testing may be waived

Finding PSGs

https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

- E.g., methylphenidate PSGs

Product-Specific Guidances for Specific Products Arranged by Active Ingredient

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Search by Active Ingredient or by RLD or RS Number

methylphenidate Search Reset

13 record(s) found for 'methylphenidate'.

Excel CSV PDF

Show 10 entries Filter:

Active Ingredient	Type	Route	Dosage Form	RLD or RS Number	Date Recommended
Methylphenidate	Draft	Transdermal	Film, Extended Release	021514	10/2018
Methylphenidate	Draft	Oral	Tablets, Extended Release, Orally Disintegrating	205489	07/2018
Methylphenidate Hydrochloride	Draft	Oral	Tablet, Extended Release	021121	07/2018
Methylphenidate Hydrochloride	Draft	Oral	Tablets, Extended Release	018029	10/2017
Methylphenidate Hydrochloride	Draft	Oral	Tablet, Chewable	207960	10/2016
Methylphenidate Hydrochloride	Draft	Oral	Capsule, Extended Release	021259	01/2016
Methylphenidate Hydrochloride	Draft	Oral	Capsule, Extended Release	205831	01/2016
Dexmethylphenidate Hydrochloride	Draft	Oral	Capsule, Extended Release	021802	03/2015
Methylphenidate Hydrochloride	Draft	Oral	Capsules, Extended Release	021284	03/2015
Methylphenidate Hydrochloride	Draft	Oral	Suspension, Extended Release	202100	12/2014

Showing 1 to 10 of 13 entries Previous 1 2 Next